Touitou discloses cosmetic or medical compositions for topical application to the skin. Touitou discloses a composition comprising 7 uci/ml tetrahydrocannabinol, 49% ethanol, 19.6% propylene glycol, and 29.4% water. Touitou further discloses that ethanol can comprise 15-30% of the composition, propylene glycol can comprise up to 20% of the composition, and water can comprise at least 20% of the composition.

Applicants, on the other hand, claim a composition comprising from about 30% to about 80% propylene glycol. Touitou only describes a composition comprising tetrahydrocannabinol and 19.6% propylene glycol. Touitou claims compositions generally comprising up to 20% propylene glycol. Nowhere does Touitou teach or describe compositions comprising tetrahydrocannabinol and propylene glycol in a concentration greater than 20% propylene glycol, especially compositions such as Applicants that comprise tetrahydrocannabinol and about 30% to about 80% propylene glycol. Thus, Touitou does not teach or suggest the subject matter of Applicant's invention.

The Office argues that "Touitou teaches a composition comprising the same constituents and amounts, and particle size of that of the instant invention, then his compositions must have the property of having a mean mass median aerodynamic diameter the range of about 1 to 10 micrometers." Office Action of January 29, 2003, at page 4. Applicants respectfully disagree. Touitou does not teach a composition comprising the same constituents and amounts as Applicants' composition, and instead, teaches away from Applicants' composition by requiring the composition comprising tetrahydrocannibinol to comprise less than 20% propylene glycol. Because Touitou's composition comprises different constituents and amounts than Applicants' composition, Touitou's compositions do not inherently have the property of having a mean mass median aerodynamic diameter in the range of about 1 to 10 micrometers.

In fact, Touitou expressly teaches away from compositions comprising tetrahydrocannibinol having a mean mass median aerodynamic diameter in the range of about 1 to 10 micrometers, stating:

> High alcoholic (organic solvent) concentration favors the production of ethosomes in nm's range while high aqueous and phospholipid concentrations favor the formation of large size ethosomes. As examples, formulation 509 (Table 4) containing 60% organic solvent and 38% water has a mean population of tens of nm's, while formulation 510 containing 50% organic solvent and 48% water has a mean population of 1 mm. In system 509 the concentration of ethanol was 48% while in formulation 510 the ethanol

> concentration is only 20%, showing that the alcohol concentration is of great importance in determining vesicle size.

Column 2, lines 26-37. Touitou correlates higher ethanol concentrations (e.g., 48% ethanol) with smaller diameters (e.g., in the tens of nm's) and lower ethanol concentrations (e.g., 20% ethanol) with larger diameters (1 mm). Touitou teaches compositions comprising tetrahydrocannibinol comprising 49% ethanol, similar to the concentration of ethanol of formulation 509 (48% ethanol). Based on these teachings, the compositions comprising tetrahydrocannibinol disclosed in Touitou are taught by Touitou to have an expected mean diameter similar to that of formulation 509, in the tens of nm's, much smaller than Applicants' particles of 1 to 10 μM. Thus, contrary to the Office's assertion, not only does Touitou not disclose compositions comprising the same constituents and amounts as Applicant's compositions, but Touitou does not disclose, and in fact teaches away, from compositions comprising particles of the same size as Applicants' claimed compositions.

Finally, Touitou teaches compositions for topical application. Touitou does not teach stable, aerosolized compositions that are pharmaceutically suitable for rapid bronchial delivery to a lung of a subject, as required by Applicants claims. As such, Applicants' claims are not made obvious by the disclosure of Touitou, as Touitou teaches away from compositions comprising tetrahydrocannabinol and greater than 20% propylene glycol with a mean mass median aerodynamic diameter from about 1 up to about 10 μM, and does not teach or suggest stable, aerosolized compositions comprising tetrahydrocannabinol that are pharmaceutically suitable for rapid bronchial delivery to a lung of a subject.

The Office relies on Patel and LaMastro to cure the deficiencies of Touitou. Because neither Patel nor LaMastro teach or suggest aerosolized compositions suitable for rapid delivery to a lung of a subject comprising the same constituents and amounts as Applicants' claimed compositions, these references are not sufficient to cure the defects of Touitou.

Finally, the Office construes Patel as teaching that the topical pharmaceutical compositions of Touitou are interchangeable with the Applicants' compositions that are pharmaceutically suitable for rapid bronchial delivery to a lung of a subject, based on the disclosure in Patel on column 26, lines 55-59, which states "The compositions of the present invention can also be formulated as a spray or an aerosol. In particular, the compositions may be formulated as a sprayable solution, and such formulation is particularly useful for spraying to coat a multiparticulate carrier, such as a bead." Applicants' respectfully disagree.

Patel does not teach or suggest stable, aerosolized compositions comprising tetrahydrocannabinol that are pharmaceutically suitable for rapid bronchial delivery to a lung of a subject. Patel discloses one type of oral composition comprising a hydrophobic active ingredient and briefly suggests that the one type of oral composition disclosed in Patel may be formulated as a spray or an aerosol. The compositions disclosed by Patel are distinct from Applicants' composition comprising tetrahydrocannibinol. Patel certainly does not teach or suggest that all oral compositions can be formulated as sprays or aerosols, or that all topical compositions can be formulated as sprays or aerosols. Regardless, Patel does not teach or suggest how such an aerosolized composition that is pharmaceutically suitable for rapid bronchial delivery to a lung of a subject would be made. Furthermore, neither Patel nor Touitou present any suggestion or motivation to combine the references of Patel and Touitou to develop compositions comprising tetrahydrocannabinol and greater than 20% propylene glycol with a mean mass median aerodynamic diameter from about 1 up to about 10 μM that are pharmaceutically suitable for rapid bronchial delivery to a lung of a subject, and neither reference teaches or suggests that such a composition would indeed result if the teachings of the references were combined.

Even if the topical compositions disclosed in Touitou could be interchanged into an aerosol form, such aerosolized compositions would not teach or suggest Applicants' aerosolized compositions, because the compositions of Touitou do not teach or suggest compositions comprising tetrahydrocannabinol that are pharmaceutically suitable for rapid bronchial delivery to a lung of a subject comprising tetrahydrocannabinol and greater than 20% propylene glycol with a mean mass median aerodynamic diameter from about 1 up to about 10 μM.

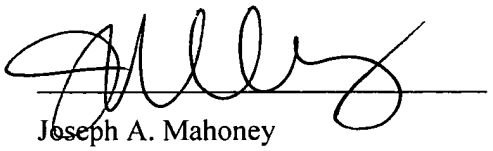
In view of the above, it is clear that Touitou in light of Patel and LaMastro does not teach or suggest the subject matter of Applicants' invention and the rejection of claims 1-4, 7-12 and 14-23 under 35 U.S.C. § 103(a) is improper and should be withdrawn.

CONCLUSION

With entry of the above Amendment and in view of the foregoing remarks, it is respectfully submitted that claims 1-4, 7-12 and 14-23 are in condition for allowance. It is respectfully submitted in view of the foregoing Amendment and Remarks that all of the objections and rejections in the Office Action dated January 29, 2003, have been overcome and should be withdrawn. Accordingly, reconsideration and withdrawal of the outstanding

rejections and allowance of claims 1-4, 7-12 and 14-23 is respectfully solicited, and the Office is respectfully requested to pass this application to issue. If, in the opinion of the Office, a telephone conference would expedite the prosecution of the subject application, the Office is invited to call the undersigned attorney.

Respectfully submitted,

Dated: March 31, 2003 By: 

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Version with Markings to Show Changes Made to the Claims

1. (Amended) A stable, aerosolizable composition [that is pharmaceutically suitable for rapid bronchial delivery to a lung of a subject], the composition comprising a therapeutically effective amount of delta-9-tetrahydrocannabinol in a pharmaceutically-acceptable semiaqueous solvent comprising volumetric ratios of about 10-70 parts of ethanol, about 10-30 parts of water and greater than about [20] 30-80 parts of propylene glycol having a combined total of 100, provided that:

(i) upon aerosolization the composition has a mean mass median aerodynamic diameter in the range from about 1 up to about 10 μM; [and]

(ii) the ratio of the ethanol, water and propylene glycol produces a stable clear solution near the solubility point of the delta-9-tetrahydrocannabinol such that upon administration to the lung, the partitioning of the delta-9-tetrahydrocannabinol from the solvent is enhanced so as to reach the bloodstream; and

(iii) the composition is pharmaceutically suitable for rapid bronchial delivery to the lung of a subject.

7. (Amended) A composition as defined in Claim 1 wherein the volumetric ratios of ethanol : water : propylene glycol are selected from those in the range of from about 10 – 70 : about 10 : greater than [20] about 30 – 80, respectively, having a combined total of 100.

23. (Amended) A stable, aerosolizable composition [that is pharmaceutically suitable for rapid bronchial delivery to a lung of a subject], the composition comprising a therapeutically effective amount of delta-9-tetrahydrocannabinol in a pharmaceutically-acceptable semiaqueous solvent comprising volumetric ratios of about 10-70 parts of ethanol,

about 10-30 parts of water and greater than about [20] 30-80 parts of a glycol selected from the group consisting of polypropylene glycol and polyethylene glycol having a combined total of 100, provided that:

(i) upon aerosolization the composition has a mean mass median aerodynamic diameter in the range from about 1 up to about 10 μM; and

(ii) the ratio of the ethanol, water and propylene glycol produces a stable clear solution near the solubility point of the delta-9-tetrahydrocannabinol such that upon administration to the lung, the partitioning of the delta-9-tetrahydrocannabinol from the solvent is enhanced so as to reach the bloodstream; and

(iii) the composition is pharmaceutically suitable for rapid bronchial delivery to a lung of a subject.

Pending Claims as of March 31, 2003

1. A stable, aerosolizable composition, the composition comprising a therapeutically effective amount of delta-9-tetrahydrocannabinol in a pharmaceutically-acceptable semiaqueous solvent comprising volumetric ratios of about 10-70 parts of ethanol, about 10-30 parts of water and greater than about 30-80 parts of propylene glycol having a combined total of 100, provided that:

(i) upon aerosolization the composition has a mean mass median aerodynamic diameter in the range from about 1 up to about 10 μM;

(ii) the ratio of the ethanol, water and propylene glycol produces a stable clear solution near the solubility point of the delta-9-tetrahydrocannabinol such that upon administration to the lung, the partitioning of the delta-9-tetrahydrocannabinol from the solvent is enhanced so as to reach the bloodstream; and

(iii) the composition is pharmaceutically suitable for rapid bronchial delivery to the lung of a subject.

2. A composition as defined in Claim 1 wherein the amount of delta-9-tetrahydrocannabinol comprises from about 0.1 to about 200 mg delta-9-tetrahydrocannabinol/mL of the solvent.

3. A composition as defined in Claim 2 wherein the amount of delta-9-tetrahydrocannabinol comprises from about 0.1 to 25 mg delta-9-tetrahydrocannabinol/mL of the solvent.

4. A composition as defined in Claim 2 wherein the amount of delta-9-tetrahydrocannabinol comprises about 50 mg delta-9-tetrahydrocannabinol/mL of the solvent.

7. A composition as defined in Claim 1 wherein the volumetric ratios of ethanol : water : propylene glycol are selected from those in the range of from about 10 – 70 : about 10 : greater than about 30 – 80, respectively, having a combined total of 100.

8. A composition as defined in Claim 7 wherein the volumetric ratios of ethanol : water : propylene glycol are about 35 : about 10 : about 55, respectively, having a combined total of 100.

9. A sterile and/or preserved sealed unit– or multi-unit dosage form of delta-9-tetrahydrocannabinol comprising a container and a stable composition for rapid delivery by inhalation to the lungs and subsequently to the bloodstream, as defined in Claim 1.

10. A sterile and/or preserved sealed unit- or multi-unit dosage form as defined in Claim 9 wherein said container comprises Type I Amber Glass

11. The composition of claim 1, wherein the mean mass median aerodynamic diameter is from about 1mM to about 3 mM.

12. The composition of claim 1, wherein the ethanol is replaced with isopropanol.

14. The composition of claim 1, wherein the amount of delta-9-tetrahydrocannabinol is from about 0.05% to about 15%, by weight, of the composition.

15. The composition of claim 14, wherein the amount of delta-9-tetrahydrocannabinol is from about 0.02% to about 5%, by weight, of the composition.

16. The composition of claim 15, wherein the amount of delta-9-tetrahydrocannabinol is from about 0.1% to about 4%, by weight, of the composition.

17. The composition of claim 1, wherein the amount of delta-9-tetrahydrocannabinol is from about 0.01 mg to about 100 mg per kilogram of body weight of the subject.

18. The composition of claim 17, wherein the amount of delta-9-tetrahydrocannabinol is from about 0.025 mg to about 35 mg per kilogram of body weight of the subject.

19. The composition of claim 18, wherein the amount of delta-9-tetrahydrocannabinol is from about 0.05 mg to about 5 mg per kilogram of body weight of the subject.

20. The composition of claim 1, further comprising an agent selected from the group consisting of an anti-oxidant, surfactant, buffer, pH adjusting agent, bacteriostatic agent, stabilizer, sodium chloride, and preservative.

21. The composition of claim 1, wherein the composition is administered to the subject one to five times a day.

22. The composition of claim 1, wherein the subject is a human.

23. A stable, aerosolizable composition, the composition comprising a therapeutically effective amount of delta-9-tetrahydrocannabinol in a pharmaceutically-acceptable semiaqueous solvent comprising volumetric ratios of about 10-70 parts of ethanol, about 10-30 parts of water and greater than about 30-80 parts of a glycol selected from the group consisting of polypropylene glycol and polyethylene glycol having a combined total of 100, provided that:

(i) upon aerosolization the composition has a mean mass median aerodynamic diameter in the range from about 1 up to about 10 μM; and

(ii) the ratio of the ethanol, water and propylene glycol produces a stable clear solution near the solubility point of the delta-9-tetrahydrocannabinol such that upon administration to the lung, the partitioning of the delta-9-tetrahydrocannabinol from the solvent is enhanced so as to reach the bloodstream; and

(iii) the composition is pharmaceutically suitable for rapid bronchial delivery to a lung of a subject.